

No new matter has been added by this amendment.

### **COMMENTS**

The invention here is both a process and a device for observing or measuring the differences found in a tissue sample -- neural or muscle -- when the sample is contacted with a chemical substance which may be useful as a medicine. By measuring and comparing the differences, the overall efficacy or the specific efficacy of a chemical substance as a medicine may be determined. In particular, the microelectrodes are coated with a collagen coating which permits measurement of the effect at a time which is considered chronic.

Claims 12-15 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 12-15 stand rejected under 35 U.S.C. §102(b) as being anticipated by Giaeever et al. (U.S. Patent No. 5,187,096). Claims 12-15 stand rejected under 35 U.S.C. §102(b) as being anticipated by Suzuki et al. (U.S. Patent No. 4,288,544). Claims 12-15 stand rejected under 35 U.S.C. §102(b) as anticipated by Nicander et al. (British Journal of Dermatology, 132; 718-724, 1995). Claims 12-15 stand rejected under 35 U.S.C. §103 as unpatentable over Nisch et al. (Biosense.Bioelect 1994, 9:737-741).

Applicants have amended this variation of the claimed invention to remove questions relating to indefiniteness of the claims and to specify with greater particularity the aspect of the invention relating to measurement of both chronic and short term effects of medicines on neural or muscle tissue.

In particular, the claims now specify that the tissue sample is a "neural or muscle" tissue sample and further, the microelectrodes are necessarily coated with a collagen covering. Further, the tissue sample is situated so that a plurality of microelectrodes contacts the tissue sample, much in the way suggested by the Examiner Office Action. It

should initially be also noted that none of the references appear to suggest the use of collagen covering on any microelectrode described in the cited articles or patents.

Rejection Under 35 U.S.C. 112

Claim 12 is rejected under 35 U.S.C. §112, second paragraph, as being vague and indefinite. The Examiner notes that claim 12 contains the recitation of “chemical substance” twice in the claim. Applicants have amended the claim to remove one of the recitation of “chemical substance”.

Claim 13 is rejected under 35 U.S.C. §112, second paragraph, for lacking antecedent basis for “said” chemical substance. Applicants have amended the claim to include “a” and remove “said” from the claim.

Claims 14 and 15 are rejected under 35 U.S.C. §112, second paragraph, as being vague and indefinite for the recitation of “arbitrary concentration”. The Examiner further notes that “the Webster’s II New Riverside University Dictionary meaning of arbitrary is ‘Determined by impulse or whim’. Therefore, it is unclear what are the metes and bounds of arbitrary concentration?”. Applicants have amended claims 14 and 15 to remove “arbitrary” and include “selected” concentration.

Withdrawal of the rejections is therefore requested.

Rejections Under 35 U.S.C. 102(b)

Claims 12-15 are rejected under 35 U.S.C. 102 (b) as anticipated by Giaever et al. (U.S. Pat. No. 5,187,096).

In support of the rejection, the Examiner notes:

"Giaever et al. describes a method which comprises a detector for detecting electrical properties of endothelial cells when chemical substance thrombin is exposed to the cultures in Figure 9 which is observed (i.e. visible property). He further describes a testing device that comprises electrical measurement portion (i.e. visible detection portions) (Figure 3, data acquisition, Figure 4, Figure 5, Figure 6 etc.). The prior art anticipates the claimed invention."

The Examiner further points out:

"Examiner would like to bring applicant's attention that claims are neither directed to a single slice of tissue nor two electrodes are able to access to a single slice of tissue. Further more, the apparatus and method of Giaever invention not only measure cultured cells but also cells that are attached to surfaces can be followed continuously and in real time. In other words, the invention can detect and measure cell attachment, cell spreading, lateral motion of cells, impedance of cell sheets, areas involved in adhesion plaques, cell-substrate spacing and vertical cell motion. (Column 3, lines 23-30). This apparatus and method can be used with human and murine fibroblasts and bovine endothelial cells (tissue) to changes in the physical environment and to drugs and other biological active compounds, under normal culture conditions., fibroblasts and endothelial cells form a sheet of tissues in culture. And also the electronics of the invention are connected to arrays of electrodes. (Column 3, lines 31-67) and multiple electrodes can be used with in the same culture chamber. Thus the prior art anticipates the claimed invention."

Applicants disagree. The claimed device and procedure both require the use of a detector comprising microelectrodes in an array on a substrate within the same culture chamber. As now amended, the tissue must contact a multiplicity of microelectrodes. Under this condition, two or more electrodes are able to access a single tissue slice and measure electrical property from different part of the tissue slice simultaneously. Giaever et al. make a comment on using multiple electrodes within the same culture chamber to obtain duplicate measurements of the same culture. They suggest that data from such measurements provide "indication of heterogeneity within the culture or average cell response". These comments indicate that Giaever et al. do not teach a method or a device

for measuring changes of electrical property of different part of the tissue slice simultaneously. Further, no mention is made of a collagen coating.

Withdrawal of rejection is therefore requested.

Claims 12-15 stand rejected under 35 U.S.C. 102 (b) as being anticipated by Suzuki et al. (U.S. Pat. No. 4,288,544). In support of the rejection, the Examiner notes:

"Suzuki et al. describe a method which comprises a detector for detecting electrical properties of different microorganisms when cultured with different media in Table 1, 2, 3, 4, 5 which is observed (i.e. visible property). He further describes a testing device that comprises electrical measurement portion (i.e. visible) visible detection portions (Figures 1 and 2, Potentiometer and Recorder). The prior art anticipates the claimed invention."

Examiner also points out that "Suzuki et al suggest that those skilled in the art can simplify remodel the device, such as to use with tissue".

Applicants disagree. The claimed device and methods require the use of a detector comprising collagen-coated microelectrodes in an array on a substrate within the same culture chamber. Suzuki et al. fails to show a multiple-electrode device which is capable of contacting with a neural or muscle tissue slice. Moreover, the Suzuki et al device is only suitable for measuring electrical property from a soup of cells in suspension. The Suzuki et al device requires a magnetic stirring bar to constantly keep the cells in suspension. Unlike the Suzuki et al device, the tissue slice must be in contact with the microelectrodes array and a stirring bar would destroy that contact. Thus, Suzuki et al teaches in the opposite direction as the present invention.

Consequently, it is quite appropriate that the rejection be withdrawn. Such withdrawal is requested.

Claims 12-15 are rejected under 35 U.S.C. 102 (b) as being anticipated by Nicander et al. 1995 (British Journal of Dermatology, 132; 718-724). In support of a rejection the Examiner notes that:

"Nicander et al discloses electrical impedance measured to five skin depths in mild irritant dermatitis induced by sodium lauryl sulphate. He uses electrical impedance measurements and also correlates those measurements with histological and visual scoring (abstract). The prior art anticipates the claimed invention."

Applicants disagree. Nicander et al does not teach use of multiple microelectrodes in an array to measure electrical property from a tissue slice cultured in a chamber.

Therefore, applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

#### Rejections Under 35 U.S.C. 103(a)

Claims 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nisch et al (Biosensors & Bioelectronics 1994, 9:737-741). In support of the rejection, the Examiner notes:

"Nisch et al. describes a method which comprises a detector for detecting electrical properties of neuronal activity in vitro. He measures a detectable electrical signal before and after stimulation in Figure 7 which is observed (i.e. visible property). He further describes a testing device comprising electrical measurement portion (i.e. visible) visible detection portion (Figure 3 - monitor, Figure 4, Figure 5, Figure 6 etc.). However, Nisch et al does not teach that the method and device are used for tissues. However, Stedman's Medical Dictionary defines tissue as 'a collection of similar cells and the intercellular substances surrounding them. There are four basic tissues in the body: 1) epithelium; 2) the connective tissue, including blood, bone, and cartilage; 3) muscle tissue; and 4) nerve tissue. In addition, while specification puts forth preferred embodiments, the specification does not define and restrict the term tissue to a particular embodiment. Therefore, based on

Stedman's Medical Dictionary the term tissue encompasses blood, which are single cells floating.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the Nisch et al method and device with a reasonable expectation of success because use of this method and device for tissue culture system are readily available. An artisan of ordinary skills would have been motivated to make such a device and method for measuring the electrical properties of tissues before and after addition of medicine or drugs because it would have helped in measuring the electrical properties of tissues before and after addition of medicine or drugs as taught by Nisch et al."

Applicants disagree. Nisch et al. does not suggest the use of or suitability for placement of a tissue slice on collagen-coated microelectrodes in an array. Applicants have amended the claims to recite neural or muscle tissue samples. Furthermore, Nisch et al does not suggest that the disclosed device or method can be combined with device or method for culturing tissue slice. Nisch et al makes no suggestion to make a device or method for introduction of a chemical substance including medicine onto the tissue slice.

Withdrawal of rejection is therefore requested.

### SUMMARY

Applicants have responded to each matter of substance raised in the Office Action. It is believed that the claims as discussed are patentable in view of the cited prior arts. Applicants request such allowance. Should the Examiner have any questions, comments, or suggestions, he is urged and invited to contact applicants' attorney at the

number listed below. Should an interview be considered desirable, please feel free to also contact applicants' attorney for a personal or telephone interview.

Respectfully submitted,

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